Pharmacology Biochemistry and Behavior, Vol. 60, No. 2, pp. 459–466, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00024-0

Effects of Food Deprivation on Conditioned Taste Aversions in Rats

S. MICHAEL BELL, TODD E. THIELE, RANDY J. SEELEY, ILENE L. BERNSTEIN AND STEPHEN C. WOODS

University of Washington, Department of Psychology, Box 351525, Seattle, WA 98195

Received 8 August 1997; Revised 4 December 1997; Accepted 4 December 1997

BELL, S. M., T. E. THIELE, R. J. SEELEY, I. L. BERNSTEIN AND S. C. WOODS. *Effects of food deprivation on conditioned taste aversions in rats.* PHARMACOL BIOCHEM BEHAV **60**(2) 459–466, 1998.—Food deprivation increases the rewarding effects of self-administered drugs such as psychomotor stimulants and benzodiazepines. These drugs also possess aversive properties and can produce conditioned tast aversions (CTA). Because drug-seeking behavior is most likely affected by both the rewarding and aversive properties of drugs, we hypothesize that food deprivation might also attenuate a drug's aversive consequences. The CTAs induced by three different drugs (amphetamine, chlordiazepoxide, and LiCl) were assessed separately. Male Long–Evans rats were assigned to one of two feeding conditions: restricted (maintained at 80% of free-feeding body weight), or nonrestricted (with ad lib food). Both groups received CTA training, consisting of an intraoral infusion of a novel saccharin solution (10 min) followed immediately by one of two IP injections: paired rats received drug, and unpaired rats received a similar volume of saline. After 10 days of ad lib food access, saccharin was presented to all rats again, and the latency to reject the tastant was used as an index of CTA learning. The rats that had been food restricted at the time of conditioning exhibited attenuated CTAs relative to those that had not been deprived. These differences were seen only when a rewarding drug (amphetamine or chlordiazepoxide) and not when a nonrewarding drug (LiCl) was used as the unconditioned stimulus. In a separate experiment, we established that this effect is apparent only when the deprivation period precedes conditioning rather than precedes testing. The present results indicate that food deprivation modulates the acquisition of a CTA induced by amphetamine or chlordiazepoxide, but not LiCl. © 1998 Elsevier Science Inc.

Conditioned taste aversion Taste aversion learning CTA Food deprivation Body weight Amphetamine Psychomotor stimulant Chlordiazepoxide Benzodiazepine Lithium chloride LiCl Reward Reinforcement Saccharin Intraoral infusion Rats

IN one of the first experiments to examine directly the effects of food deprivation on drug intake, Meisch and Thompson (30) found that food-restricted rats consumed more ethanol than rats fed ad lib [see also (1,43,45). Some investigators interpreted these findings to indicate that food-deprived rats consumed the additional ethanol as a ready source of caloric replenishment, rather than as an agent that interacted with food deprivation psychopharmacologically (27). This hypothesis was consistent with the observation that rates of ethanol self-administration substantially decrease following the reinstatement of ad lib food (1,35,45).

Over the years, several laboratories have questioned this "Caloric Hypothesis." For example, Carroll et al. (6) and Meisch and Kliner (31) observed robust food deprivation-induced elevations in drug self-administration, even when the drugs did not provide calories. For example, etonitazene, a potent noncaloric opioid, is self-administered to a greater degree when rats are food deprived, and these increases are apparent regardless of whether the rat self-administers the drug orally or intravenously (6,31). Numerous studies have demonstrated a broad generality to these findings: psychomotor stimulants (8,12,13), depressants (25,30), opioids (6–8), arylcyclohexylamines (7,8), and nicotine and cannabis (13,42) are all self-administered at higher levels when animals are food deprived. These effects are consistent across routes of administration and across species [for a review, see (9)].

It has been hypothesized that, rather than self-administering drugs to compensate for needed calories or to compensate for decreased body weight, food-deprived rats self-administer drugs at higher rates because the reinforcing efficacy of the

Requests for reprints should be addressed to S. Michael Bell, University of Washington, Department of Psychology, Box 351525, Seattle, WA 98195.

drugs is increased in states of deprivation (6,31). We recently provided evidence supporting this hypothesis. Using conditioned place preference as an indication of the rewarding properties of cocaine, we found that food deprivation increased cocaine-induced place preference learning in rats (4). Thus, cocaine produces a preference for the environment in which it was administered, and this preference is strengthened by a period of food deprivation.

Although evidence indicates that many commonly abused and self-administered psychoactive substances possess rewarding properties, there is also evidence that many of these same drugs have aversive properties. For example, when consumption of a novel saccharine flavor was paired with an injection of amphetamine (AMPH), it was observed that rats subsequently avoided the saccharine solution, indicating the development of an AMPH-induced conditioned taste aversion [CTA; (41)]. This has been interpreted to suggest that the drug (in this case, AMPH) that was paired with the taste possesses "aversive" properties. Interestingly, morphine, AMPH, and ethanol are each capable of establishing a CTA at doses that support operant self-administration, even when experimental conditions are controlled such that the drugs are administered in the same manner and at the same dose in both paradigms (16,22). In fact, both morphine and AMPH can simultaneously serve as a positive reinforcer and induce a CTA (36,46). Further, drugs that produce conditioned place preferences and that are self-administered as positive reinforcers can also produce conditioned place aversions (2,3,5,15,23,29, 39–40).

Evidence suggests that increased self-administration of drugs during food-deprived states may be due to the increased reinforcing efficacy of the drug. Because both the rewarding and aversive properties of drugs likely influence drug-seeking behavior, an additional possibility is that increased drug self-administration during food-deprived states may reflect an attenuation of the aversive properties associated with the drug. To test this possibility, we assessed the ability of food deprivation to attenuate AMPH-induced CTAs. We hypothesized that if food deprivation reduces the magnitude of the aversive properties associated with AMPH, then this decrement should be reflected by an attenuated CTA. To assess the generality of this phenomenon, we also examined the effects of food deprivation on CTAs produced by chlordiazepoxide (CDPX), a benzodiazepine, and on CTAs produced by lithium chloride, a potent toxin possessing no known rewarding value.

METHOD

Subjects

Adult male Long–Evans rats from the breeding colony of the Department of Psychology at the University of Washington were individually housed in hanging stainless steel cages within a colony room that was maintained on a 12 L:12 D cycle (lights on at 0700 h). Water was available ad lib, and unless otherwise stated, pelleted Harlan Teklad rodent diet (#8604) was also freely available.

Surgery and Apparatus

Surgical procedures were adapted from those developed by Grill and associates to assess and the physiological mechanisms underlying CTA (20,21). We implanted rats with unilateral intraoral cannulae constructed of PE-100 tubing with a heat flare at one end. The rats were anesthetized with an intraperitoneal injection of Ketamine (86 mg/kg)/Xylazine (12.9 mg/kg). The cannula was inserted anterolateral to the first maxillary molar and routed subcutaneously to exit midsaggitally at the top of the head. The cannula was secured with washers fashioned from Teflon sheeting. All rats were treated prophylactically with 0.2 ml Gentamicin intramuscularly.

The observation chamber was also adapted from that developed by Grill & Norgren (20,21) and was constructed from a clear Plexiglas cylinder (22.2 cm i.d. $\times$ 25.4 cm long). The chamber rested on end upon a Plexiglas base that was mounted above a mirror placed at a 45 angle, such that the ventral aspect of the animal could be easily viewed during the sessions. All sessions were viewed remotely via a video link. An infusion pump with a 5-ml syringe was mounted above the chamber and was used to infuse fluids through the PE tubing and into each rat's oral cavity at a rate of 0.5 ml/min.

Rats were allowed approximately 1 month to recover from surgery and were then habituated to the test chambers and the infusion process. Habituation to the apparatus consisted of placing a rat in the chamber for two 30-min sessions. Additional habituation to the apparatus, and habituation to the infusion process, consisted of placing the rats in the chamber and intraorally delivering tap water during the first 10 min on two additional 30-min sessions.

Drugs and Solutions

Sodium saccharin, *d*-amphetamine HCl (AMPH), chlordiazepoxide HCl (CDPX), and lithium chloride (LiCl) were purchased from Sigma Chemical (St. Louis, MO). Saccharine solutions (0.15%) were made with nonsterile deionized/distilled water. AMPH (2.5 mg/ml) and CDPX (10 mg/ml) were dissolved in sterile saline. LiCl (0.15 M) was dissolved in sterile water. Concentrations of all compounds are expressed in terms of the salt. Relatively high drug doses were chosen [see, e.g., (28)] to match the severity of CTA produced by our standard LiCl dose. Specifically, 3.0 mg/kg AMPH and 20 ml/kg LiCl produce comparable CTAs (41). Using data published by Gamzu [(17); see Fig. 3, p. 486], we selected a dose of CDPX (15 mg/kg) that would approximate the magnitude of the CTA produced by these doses of AMPH and LiCl.

Statistics

All statistics were carried out according to the principles described by Winer et al., (47). The mean body weights of restricted and ad lib animals were compared at three separate points (predeprivation, training, and testing) using two-sample *t*-tests. To assess *CTAs, 2* $\times$ 2 (group $\times$ feed) ANOVAs were computed. The "group" factor examined differences between groups that had the drug injection either paired or unpaired with the saccharine infusion on the conditioning day. The "feed" factor examined differences between restricted and ad lib groups. Because we hypothesized that a difference would be apparent between rats assigned to the different feeding conditions, a planned comparison between paired groups within each drug condition was computed using a one-way ANOVA.

Procedure

The CTAs induced by three different drugs (AMPH, CDPX, and LiCl) were assessed. Conditioning and testing with each of these drugs was carried out separately (see Table 1 for a summary of group sample sizes). After the surgeries, recovery periods, and habituation procedures were completed, the rats within each drug condition were assigned to

TABLE 1
SAMPLE SIZES FOR EACH GROUP

Group	Drug Used to Induced Conditioned Taste Aversion			
	Amphetamine	Chlordiazepoxide	Lithium Chloride	Amphetamine*
Restricted				
Paired	11	10	11	10
Unpaired	5	4	6	4
Ad Libitum				
Paired	10	10	9	10
Unpaired	5	4	5	4

*Indicates the secondary experiment, when the period of food-deprivation followed, rather than preceded, conditioning.

one of two groups: ad lib or restricted. Feeding conditions were not altered for the ad lib group, but rats in the restricted group were limited to 5 to 8 g of food per day over a 7-day period. This regimen is based upon methods used in studies investigating the effects of food deprivation on the reinforcing properties of drugs [see (4,9)] and results in a significant loss of body weight by the restricted animals over 7 days.

During conditioning, rats were placed in the observation chamber and infused with 5 ml of a novel saccharin solution. The rats were videotaped and the amount of time (s) that passed before the rat rejected the fluid (passively or actively) was recorded. Following the 10-min infusion period the rats were injected intraperitoneally with one of two solutions. Paired rats received the drug, and unpaired rats received a similar volume of sterile saline. To control for nonspecific drug effects, the rats within each group were injected with the alternate solution 24 h later; the rats were not placed in the testing chamber, nor was there a saccharine infusion given on this day. One hour following this second injection, the restricted rats were again allowed free access to food. Ten days following the conditioning sessions the rats were tested. They were placed in the conditioning chambers and again infused with 5 ml of saccharine solution for 10 min, videotaped, and the latency to first fluid rejection was assessed.

An additional experiment was conducted to assess the time-specific effects of the period of food deprivation on AMPH-induced CTAs. The methods were identical to those described above, except for the following: initially both groups of rats were allowed ad lib access to food prior to and during conditioning. Three days following conditioning, the rats were assigned to one of two conditions: ad lib or restricted. Feeding conditions were not altered for the ad lib group, but rats in the restricted group were limited to 5 to 8 g of food per day over a 7-day period. On the final day of this period (i.e., 10 days following the conditioning sessions and 7 days following initiation of the deprivation period) the rats were tested. Thus, the rats in this experiment were exposed to the same degree of food deprivation, both in terms of duration and severity, but here the deprivation period preceded testing rather than conditioning.

RESULTS

Amphetamine

Before surgery the rats ranged in body weight from 369 to 534 g, and following surgery all rats lost weight slowly for approximately 7 days, with an average loss of 7.0%. By the initiation of the food-deprivation regimen, all the rats had reattained their presurgical body weight baselines, and averaged 4.7% above it. Two groups were then created (see Fig. 1A) such that prior to the deprivation regimen their mean body weights did not differ reliably: ad lib (438 ± 10 g) vs. restricted (451 ± 12 g). However, within 7 days the restricted rats had lost a substantial amount of weight (on average, 20.0% below their predeprivation body weights) and the weights of the two groups differed statistically: ad lib (445 ± 9 g) vs. restricted (361 ± 10 g); $t(29) = 6.00$, $p < 0.001$. Within the 10 days following conditioning both groups of rats gained in body weight, although for the restricted rats the rate was substantially greater, such that on the test day the weights of the two groups no longer differed statistically: ad lib (465 ± 11 g) vs. restricted (451 ± 13 g).

On the conditioning day saccharin was ingested throughout all or most of the 10-min infusion period, and there were no differences among any of the groups in their latencies to drip. Conversely, on the test day, groups that had received injections of AMPH paired with saccharin demonstrated significant CTAs (see Fig. 1B). Relative to their respective unpaired controls, both restricted and ad lib rats rejected saccharin earlier in the session. An ANOVA revealed a significant effect, $F(1, 30) = 23.22$, $p < 0.001$, that indicated the paired groups (restricted/paired and ad lib/paired) differed from the unpaired groups (restricted/unpaired and ad lib/unpaired). However, neither the feeding condition nor the interaction achieved statistical significance. Conversely, a planned comparison of the paired groups did indicate that the CTA of the restricted rats was significantly weaker than that of the ad lib rats, $F(1, 20) = 5.701$, $p < 0.03$.

Chlordiazepoxide

Before surgery the rats ranged in body weight from 258 to 307 g, and following surgery all rats lost weight slowly for approximately 7 days, with an average loss of 7.3%. By the initiation of the food-deprivation regimen, all the rats had reattained their presurgical body weight baselines, and averaged 35% above it. Two groups were then created (see Fig. 2A) such that prior to the deprivation regimen their mean body weights did not differ reliably: ad lib (382 ± 8 g) vs. restricted (382 ± 9 g). However, within 7 days the restricted rats had lost a substantial amount of weight (on average, 23% below their predeprivation body weights) and the body weights of the two groups differed statistically: ad lib (395 ± 12 g) vs. restricted (294 ± 8 g); $t(27) = 7.05$, $p < 0.001$. Within the 10 days following conditioning both groups of rats gained in body weight,

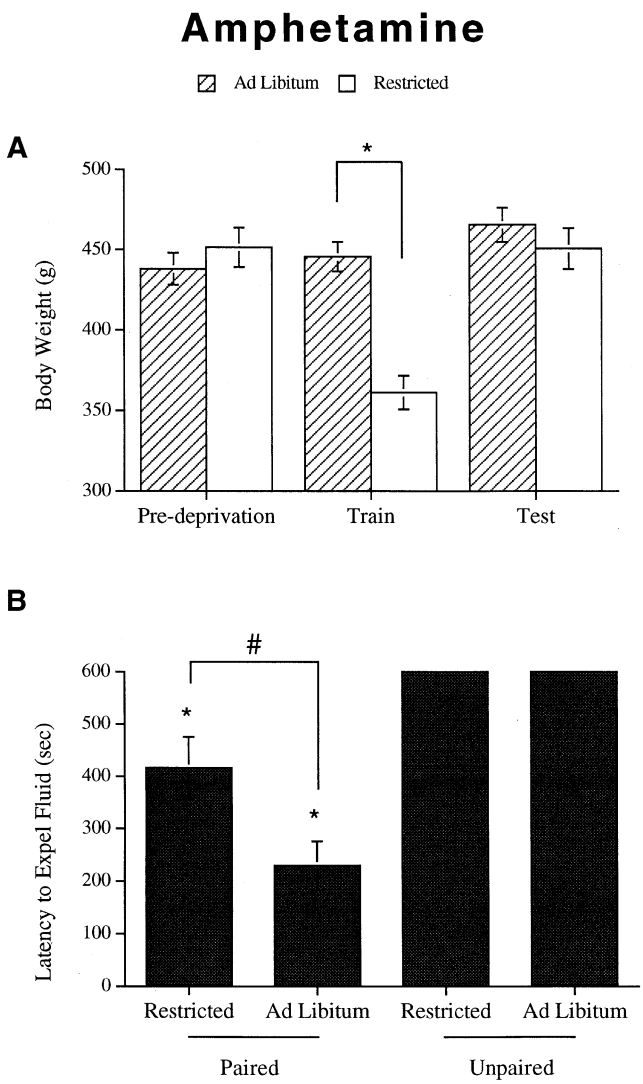

FIG. 1. (A) Mean body weights (±SEM) of rats prior to, during, and following conditioning; *indicates that the two groups differed significantly from each other, $p < 0.001$. Lack of asterisks indicates the two groups did not significantly differ ($\alpha = 0.05$). (B) Mean latency to drip (±SEM) introrally infused saccharin during the test day of the conditioning experiment; *indicates that the US-CS paired groups differed significantly relative to their unpaired controls, $p < 0.001$; #indicates that the two paired groups differed significantly from each other, $p < 0.03$.

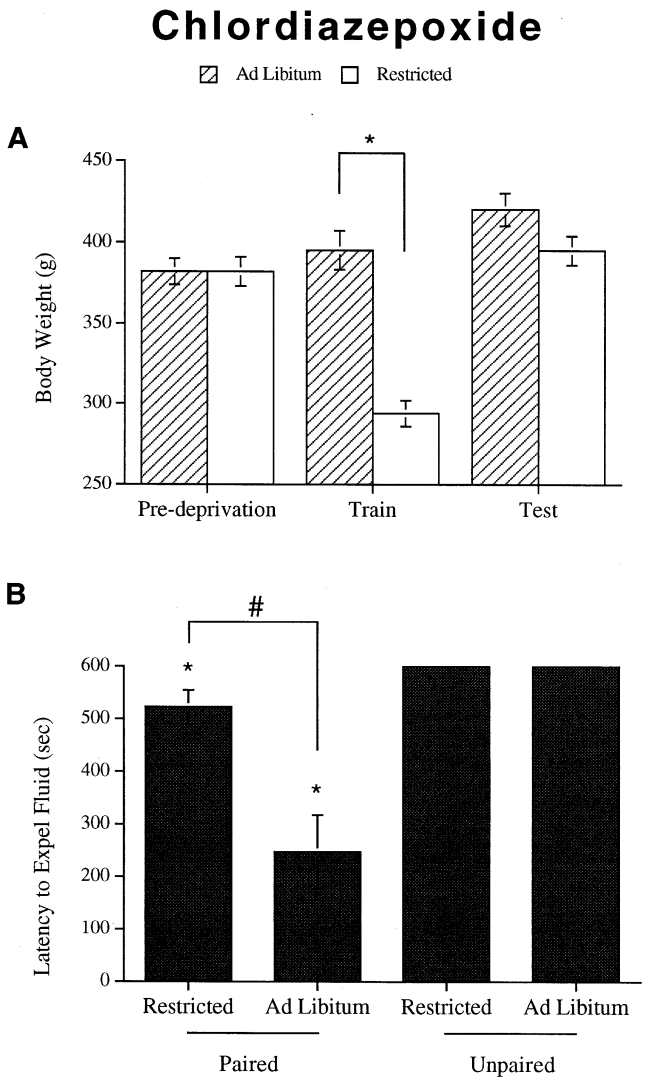

FIG. 2. (A) Mean body weights (±SEM) of rats prior to, during, and following conditioning; *indicates that the two groups differed significantly from each other, $p < 0.001$. Lack of asterisks indicates the two groups did not significantly differ ($\alpha = 0.05$). (B) Mean latency to drip (±SEM) introrally infused saccharin during the test day of the conditioning experiment; *indicates that the US-CS paired groups differed significantly relative to their unpaired controls, $p < 0.001$; #indicates that the two paired groups differed significantly from each other, $p < 0.002$.

though for the restricted rats the rate was substantially greater, such that on the test day the weights of the two groups no longer differed significantly: ad lib (420 ± 10 g) vs. restricted (395 ± 9 g).

On the conditioning day saccharin was ingested throughout all or most of the 10-min infusion period, and there were no differences among any of the groups in their latencies to drip. Conversely, on the test day, groups that had received injections of CDPX paired with saccharin demonstrated significant CTAs (see Fig. 2B). Relative to their respective unpaired controls, both restricted and ad lib rats rejected saccharin earlier in the session. An ANOVA revealed a significant effect, $F(1, 27) = 11.86$, $p < 0.002$, that indicated the paired groups (restricted/paired and ad lib/paired) differed from the unpaired groups (restricted/unpaired and ad lib/unpaired). Additionally, there was also an effect of feeding condition, $F(1, 27) = 4.83$, $p < 0.05$, and interaction between the two variables, $F(1, 27) = 4.83$, $p < 0.05$. Furthermore, a planned comparison of the paired groups indicated that the CTA of the restricted rats was significantly weaker than that of the ad lib rats, $F(1, 19) = 12.68$, $p < 0.002$.

Lithium Chloride

Before surgery the rats ranged in body weight from 314 to 457 g, and following surgery all rats lost weight slowly for approximately 7 days, with an average loss of 7.7%. By the initi-

ation of the food-deprivation regimen, all the rats had reattained their presurgical body weight baselines, and averaged 16.4% above it. Two groups were created (see Fig. 3A) such that prior to the deprivation regimen their mean body weights did not differ reliably: ad lib (449 ± 12 g) vs. restricted (446 ± 12 g). However, within 7 days the restricted rats had lost a substantial amount of weight (on average, 17.2% of their predeprivation body weights) and the weights of the two groups differed statistically: ad lib (461 ± 13 g) vs. restricted (369 ± 11 g); $t(29) = 5.36$, $p < 0.001$. Within the 10 days following conditioning, both groups of rats gained in body weight, although for the restricted rats the rate was substantially greater, such that on the test day the weights of the two groups no longer differed statistically: ad lib (465 ± 16 g) vs. restricted (433 ± 13 g).

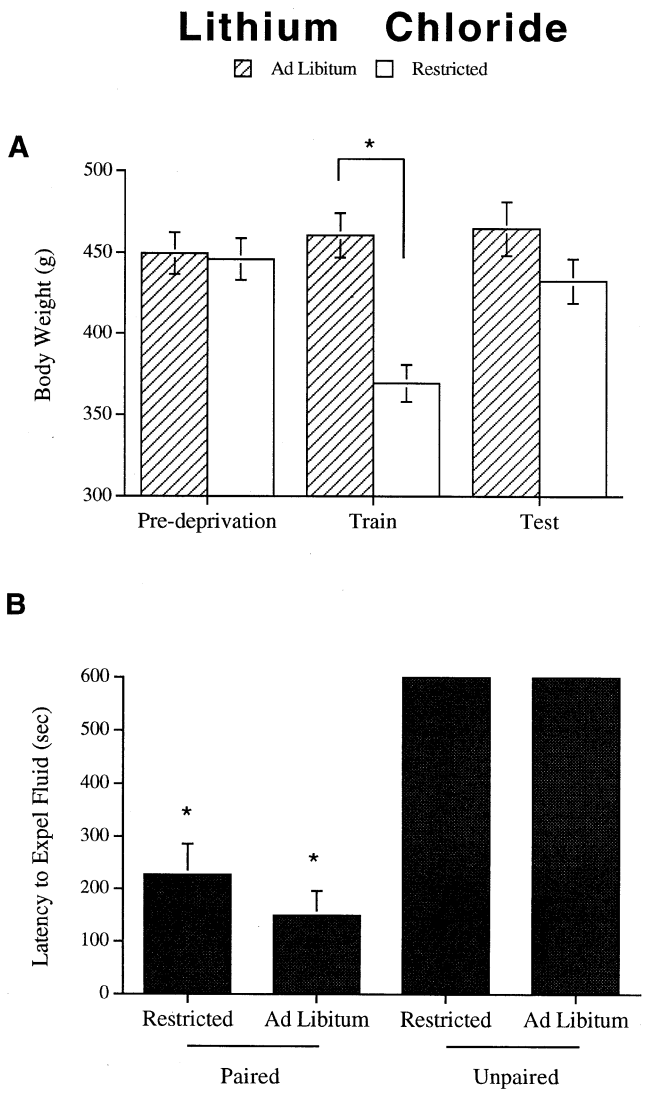

FIG. 3. (A) Mean body weights (±SEM) of rats prior to, during, and following conditioning; *indicates that the two groups differed significantly from each other, $p < 0.001$. Lack of asterisks indicates the two groups did not significantly differ ($\alpha = 0.05$). (B) Mean latency to drip (±SEM) introrally infused saccharin during the test day of the conditioning experiment; *indicates that the US-CS paired groups differed significantly relative to their unpaired controls, $p < 0.001$. Lack of pound sign indicates the two groups did not significantly differ ($\alpha = 0.05$).

On the conditioning day saccharin was ingested throughout all or most of the 10-min infusion period, and there were no differences among any of the groups in regard to their latency to drip. Conversely, on the test day, groups that had received injections of LiCl paired with saccharin demonstrated significant CTAs (see Fig. 3B). Relative to their respective unpaired controls, both restricted and ad lib rats rejected saccharin earlier in the session. An ANOVA revealed a significant effect, $F(1, 30) = 66.15$, $p < 0.001$, that indicated the paired groups (restricted/paired and ad lib/paired) differed from the unpaired groups (restricted/unpaired and ad lib/unpaired). However, neither the feeding condition, nor the interaction, nor the planned comparison of the paired groups achieved statistical significance. Thus, while food deprivation attenuated the CTAs induced by rewarding drugs (i.e., AMPH and CDPX), it did not affect the CTA produced by the nonrewarding drug, lithium chloride.

Timing of Deprivation Period

Before surgery rats ranged in body weight from 292 to 390 g, and following surgery all of the rats lost weight slowly for approximately 7 days, with an average loss of 7.1%. Prior to the initiation of the food-deprivation regimen, all the rats had reattained their presurgical body weight baselines, and averaged 8.7% above it. Two groups were created (see Fig. 4A) such that prior to conditioning the two groups did not reliably differ in body weight: ad lib (372 ± 8 g) vs. restricted (378 ± 8 g). The groups did not differ reliably from each other prior to the deprivation regimen as well: ad lib (371 ± 9 g) vs. restricted (379 ± 8 g). However, by the test day, 7 days later, the restricted rats had lost a substantial amount of weight (on average, 19.1% of their predeprivation body weights) and the weights of the two groups differed statistically: ad lib (383 ± 13 g) vs. restricted (306 ± 6 g); $t(26) = 5.29$, $p < 0.001$.

On the conditioning day, saccharin was ingested throughout all or most of the 10-min infusion period, and there were no differences among any of the groups in regard to their latency to drip. Conversely, on the test day, groups that had received injections of AMPH paired with saccharin demonstrated significant CTAs (see Fig. 4B). Relative to their respective unpaired controls, both restricted and ad lib rats rejected saccharin earlier in the session. An ANOVA revealed a significant effect, $F(1, 27) = 23.50$, $p < 0.001$, that indicated the paired groups (restricted/paired and ad lib/paired) differed from the unpaired groups (restricted/unpaired and ad lib/unpaired). Neither the feeding condition, nor the interaction, nor the planned comparison of the paired groups achieved statistical significance. Thus, a decrease in strength of AMPH-induced CTA is specifically due to food deprivation effects on the drug at the time of conditioning, and not due to the food deprivation per se.

DISCUSSION

Consistent with previous research, we have found that rats develop taste aversions to intraorally infused saccharin when the taste is followed by an intraperitoneal injection of AMPH, CDPX, or LiCl (16–18,22,33,36,37,40). We have additionally found that if rats are food deprived to approximately 80% of their free-feeding body weights on and before the day of conditioning, both AMPH-induced and CDPX-induced CTAs are attenuated. This is indicated by the significantly longer latencies to expel a fluid that had been previously paired with

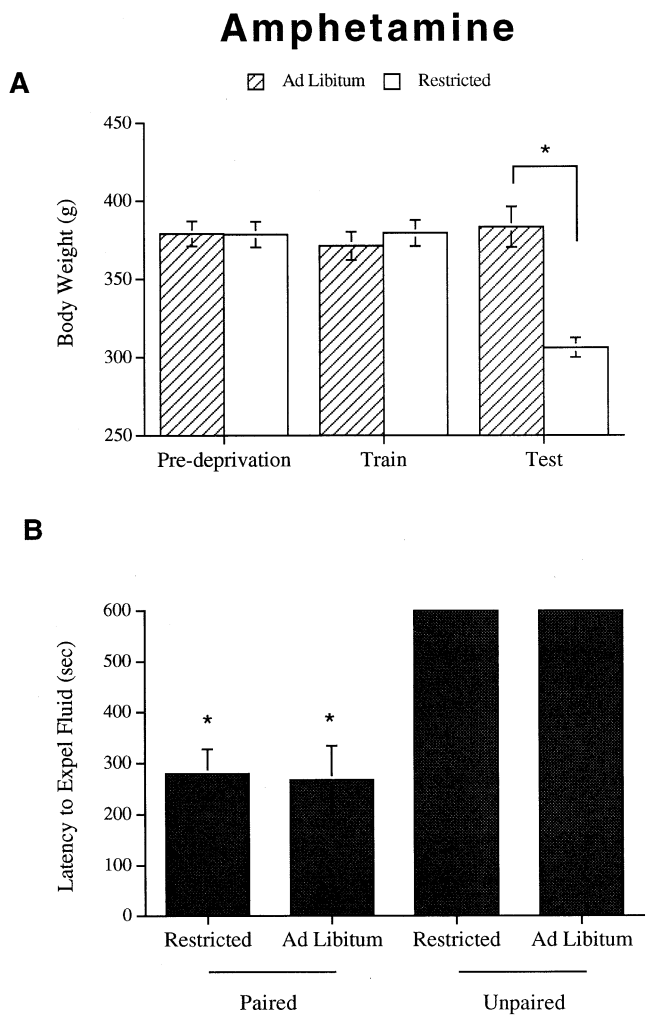

FIG. 4. (A) Mean body weights (±SEM) of rats prior to, during, and following conditioning; *indicates that the two groups differed significantly from each other, $p < 0.05$. Lack of asterisks indicates the two groups did not significantly differ ($\alpha = 0.05$). (B) Mean latency to drip (±SEM) introrally infused saccharin during the test day of the conditioning experiment; *indicates that the US-CS paired groups differed significantly relative to their unpaired controls, $p < 0.05$. Lack of pound sign indicates the two groups did not significantly differ ($\alpha = 0.05$).

either AMPH or CDPX in the food-deprived rats relative to their nondeprived controls.

Even though studies have not previously examined the interaction between feeding states and the CTAs produced by drugs considered to have rewarding properties, our results were predicted on the basis of other research that focused upon the effects of food deprivation. Numerous studies have demonstrated that food deprivation increases the reinforcing efficacy of commonly abused drugs. This effect has been demonstrated across drug classes, routes of administration, schedules of reinforcement, species, and paradigms (4,9). Given that food deprivation appears to increase the rewarding properties of drugs of abuse, and assuming that drug-seeking behavior is influenced by both the rewarding and aversive properties of drugs, we hypothesized that there would be a corresponding decrease in the aversive properties of these same drugs. Our results indicate that, at least as measured by CTA learning, the aversive effects of AMPH and CDPX are attenuated by food deprivation.

Conventional CTA paradigms, such as a one- or two-bottle test, usually require a period of water deprivation that precedes the test to induce the rat to drink during a specified period. Use of fluid deprivation would have compromised our experimental design by causing our nonrestricted controls to be deprived in other ways (i.e., water deprived). Thus, we chose to use the methods Grill and associates developed to assess the physiological mechanisms underlying CTA (20,21). These particular methods have the advantage of not requiring the rat to approach and actively drink a test solution. Instead, the conditioned stimulus is directly infused into the rat's mouth and the rat need only to ingest or expel the fluid. Finally, because a rat is required to both approach and consume a test solution in conventional CTA paradigms, some have argued that these tests are methods that assess avoidance more than aversion (21,32). Our intention was to focus on the aversive components of drugs per se.

The present results suggest that the aversive effects of rewarding drugs (i.e., AMPH and CDPX) can be modulated by food deprivation, yet other possibilities need to be considered. It is possible that because nonrestricted rats were trained and tested in the same feeding state, while the restricted rats were not, weaker aversions in the latter group could represent a state-dependent learning effect. Alternatively, it is possible that the period of food deprivation led to an enhancement of saccharin preference that was obscured by a ceiling effect in unpaired animals, yet revealed in paired animals. We do not believe these are likely explanations of our findings because similar effects would have been expected when a drug such as LiCl was used as the unconditioned stimulus, and this was not the case.

Food deprivation was not associated with weaker LiCl-induced CTAs. Peck and Ader (33), using a two-bottle choice CTA paradigm and another drug assumed to possess no rewarding properties (cyclophosphamide), obtained evidence suggesting that rats maintained on ad lib water developed stronger CTAs than rats that were water deprived throughout both the conditioning and testing periods. However, when Revusky et al. (37) attempted to replicate those findings, they did not obtain the same results. Instead, these researchers concluded that cyclophosphamide and LiCl induced similar CTAs, regardless of whether the rats had been deprived or not. Gillete et al. (18) also reported that comparable LiCl-induced aversions were displayed regardless of food or water deprivation states. In a set of experiments using deprivation periods similar to those used here, Peck and Ader (33) obtained results analogous to ours. That is, they observed no differences in LiCl-induced CTAs between deprived and nondeprived rats when the deprivation period was limited to either the pre- or the postconditioning periods. Finally, we observed that the severity of the LiCl-induced CTA shown by our paired ad lib control rats was consistent with what we have seen previously (38,41,44). Further, these CTAs did not reliably differ from those produced in the paired food-restricted rats. Thus, the ability of food deprivation to modulate a CTA appears to be specific to drugs possessing rewarding properties.

Pothos et al. (34), have shown that animals that have been chronically starved undergo selective depression of their mesoaccumbens dopamine systems. Consistent with this, Figlewicz et al. (14) have shown that chronic treatments of insulin increases dopamine transporter mRNA levels. These data suggest that food deprivation in general may affect the plasticity

of selective neural circuits. However, in our final experiment we addressed the timing of the deprivation period and showed that a decrease in strength of AMPH-induced CTA is specifically due to food-deprivation effects on the drug at the time of conditioning. A period of food deprivation of equal severity and duration that preceded testing (rather than conditioning) did not affect the severity of the resulting AMPH-induced CTA. Thus, it appears that for food deprivation to modulate CTA learning the related physiological changes, for example, selective alterations of the mesolimbic dopaminergic system, must be neurologically integrated on or before the time of conditioning.

In summary, there are several potential explanations for the present results that are easily discounted. State-dependent learning cannot account for the effect of food deprivation to attenuate AMPH-induced or CDPX-induced CTAs, because such a mechanism would have also interfered with the LiCl-induced CTA, and this was not the case. For the same reasons, it is not likely that either food deprivation in general or nonspecific residual effects associated with the food deprivation interfered with the retention of the AMPH-induced CTA. We can also discount the possibility that food deprivation attenuated the ability of rewarding drugs to produce a CTA because of phenomena specific to the pharmacological classes. Specifically, because both AMPH- and CDPX-induced CTAs were attenuated following a period of food-deprivation, it seems unlikely that this could be attributed to either the ability of the psychomotor stimulant to reduce hunger [see (24,26) or to the ability of benzodiazepine to induce feeding [see (10,11)].

We have advanced the hypothesis that food deprivation modulates both the rewarding and aversive properties of drugs that possess the potential for abuse. An alternative hypothesis has recently been proposed by Grigson (19), who reinterprets the apparently paradoxical observation that reinforcing drugs appear to produce CTAs. Grigson suggests that rats decrease intake of a gustatory conditioned stimulus following taste–drug pairings not because they have developed CTAs, but rather because the rewarding properties of the gustatory stimulus pale in comparison to those of the anticipated drug of abuse. This has been labeled an anticipatory contrast effect (19). Such an interpretation of our data would suggest that the rewarding value of saccharin for a hungry rat would be increased, and hence, the contrast between this saccharine solution and the anticipated drug (AMPH or CDPX) would be reduced. This is consistent with our findings of an effect of deprivation state at the time of conditioning, but it is not necessarily consistent with our findings of a lack of such an effect when the deprivation period preceded testing.

In conclusion, we present evidence that food deprivation can attenuate the aversive properties of the reinforcing drugs AMPH and CDPX, as measured in the CTA paradigm. This evidence adds to the already large body of literature indicating that food deprivation enhances the reinforcing properties of drugs.

ACKNOWLEDGEMENTS

This work was supported by NIH Grants AA 07455, DK 35816, DC 00248, and DK 17844.

REFERENCES

1. Ashkenasy-Lelu, P.: L'alcoolisation chronique experimentale. Influence exercee par divers facteurs physiologiques sur la consommation spontanee d'alcool chez les animaux de laboratoire. Ann. Nutr. Aliment. 14:101–133; 1960.
2. Barr, G. A.; Paredes, W.; Bridger, W. H.: Place conditioning with morphine and phencyclidine: Dose dependent effects. Life Sci. 36: 363–368; 1985.
3. Bechara, A.; van der Kooy, D.: Opposite motivational effects of endogenous opioids in brain and periphery. Nature 314:533–534; 1985.
4. Bell, S. M.; Stewart, R. B.; Thompson, S. C.; Meisch, R. A.: Food deprivation increases cocaine-induced conditioned place preference and locomotor activity in rats. Psychopharmacology (Berlin) 31:1–8; 1997.
5. Best, P. J.; Best, M.R.; Mickley, G. A.: Conditioned aversion to distinct environmental stimuli resulting from gastrointestinal distress. J. Comp. Physiol. Psychol. 85:250–257; 1973.
6. Carroll, M. E.; France, C. P.; Meisch, R. A.: Food deprivation increases oral and intravenous drug intake in rats. Science 205: 319–321; 1979.
7. Carroll, M. E.; France, C. P.; Meisch, R. A.: Intravenous self-administration of etonitazene, cocaine an phencyclidine in rats during food-deprivation and satiation. J. Pharmacol. Exp. Ther. 217:241–247; 1981.
8. Carroll, M. E.; Stotz, D. C.: Oral d-amphetamine and ketamine self-administration by rhesus monkeys: Effects of feeding conditions. J. Pharmacol. Exp. Ther. 227:28–34; 1983.
9. Carroll, M. E.; Meisch, R. A.: Increased drug-reinforced behavior due to food deprivation. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Advances in behavioral pharmacology. New York: Elseviar; 1984:349–381.
10. Cooper, S. J.; Moores, W. R.: Benzodiazepine-induced hyperphagia in the nondeprived rat: Comparisons with CL 218,872, zopiclone, tracazolate and phenobarbital. Pharmacol. Biochem. Behav. 23:169–172; 1985.
11. Cooper, S. J.; Yerbury, R. E.: Midazolam-induced hyperphagia and FG 7142-induced anorexia: Behavioral characteristics in the rat. Pharmacol. Biochem. Behav. 25:99–106; 1986.
12. de la Garza, R.; Bergman, J.; Hartel, C. R.: Food deprivation and cocaine self-administration. Pharmacol. Biochem. Behav. 15:141–144; 1981.
13. de la Garza, R.; Johanson, C. E.: The effects of food deprivation on the self-administration of psychoactive drugs. Drug Alcohol Depend. 19:17–27; 1987.
14. Figlewicz, D. P.; Szot, P.; Chavez, M.; Woods, S. C.; Vieth, R. C.: Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra. Brain Res. 644:331–334; 1984.
15. Fudala, P. J.; Iwamoto, E. T.: Conditioned aversion after delay place conditioning with nicotine. Psychopharmacology (Berlin) 92:376–381; 1987.
16. Gamzu, E.; Vincent, G.; Boff, E.: A pharmacological perspective of drugs used in establishing conditioned taste aversions. Ann. NY Acad. Sci. 443:231–249; 1984.
17. Gamzu, E.: The multifaceted nature of taste-aversion-inducing agents: Is there a single common factor? In: Barker, L. M.; Best, M. R.; Domjan, M., eds. Learning mechanisms in food selection. Waco, TX: Baylor University Press; 1978:477–509.
18. Gillette, K.; Bellingham, W. P.; Martin, G. M.: Transfer of a taste aversion from food to water under various states of deprivation. Anim. Learn. Behav. 7:441–446; 1979.
19. Grigson, P. S.: Conditioned taste aversions and drugs of abuse: A reinterpretation. Behav. Neurosci. 111:129–136; 1977.
20. Grill, H. J.; Norgren, R.: The taste reactivity test I: Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 143:263–279; 1978.
21. Grill, H. J.: Physiological mechanisms in conditioned taste aversions. Ann. NY Acad. Sci. 443:67–88; 1978.
22. Hunt, T.; Amit, Z.: Conditioned taste aversion induced by self-administered drugs: Paradox revisited. Neurosci. Lett. 172:1–5; 1987.

23. Iwamoto, E. T.: Place-aversion conditioned by phencyclidine in rats: Development of tolerance and pharmacological antagonism. Alcohol Drug Res. 6:265–276; 1986.
24. Kanarek, R. B.; Glick, A. L.; Marks-Kaufman, R.: Dietary influences on the acute effects of anorectic drugs. Physiol. Behav. 49: 149–152; 1991.
25. Kliner, D. J.; Meisch, R. A.: The effects of food deprivation and satiation on oral pentobarbital self-administration in rhesus monkeys. Pharmacol. Biochem. Behav. 16:579–584; 1982.
26. Koob, G. F.; Riley, S. J.; Smith, S. C.; Robbins, T. W.: Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J. Comp. Physiol. Psychol. 92:917–927; 1978.
27. Lester, D.; Freed, E. X.: A rat model of alcoholism? Ann. NY Acad. Sci. 197:54–59; 1972.
28. Lin, H. Q.; McGregor, I. S.; Atrens, D. M.; Christie, M. J.; Jackson, D. M.: Contrasting effects of dopaminergic blockade on MDMA and d-amphetamine conditioned taste aversions. Pharmacol. Biochem. Behav. 47:369–374; 1994.
29. Martin, J. C.; Ellinwood, E. H.: Conditioned aversion in spatial paradigms following methamphetamine injection. Psychopharmacologia 36:323–335; 1974.
30. Meisch, R. A.; Thompson, T.: Ethanol as a reinforcer: Effects of fixed-ratio size and food deprivation. Psychopharmacologia 28: 171–183; 1973.
31. Meisch, R. A.; Kliner, D. J.: Etonitazene as a reinforcer for rats: Increased etonitazene-reinforced behavior due to food-deprivation. Psychopharmacology (Berlin) 63:97–98; 1979.
32. Parker, L. A.: Rewarding drugs produce taste avoidance, but not taste aversions. Neurosci. Biobehav. Rev. 19:143–157; 1995.
33. Peck, J. H.; Ader, R.: Illness-induced taste aversion under states of deprivation and satiation. Anim. Learn. Behav. 2:6–8; 1974.
34. Pothos, E. N.; Creese, I.; Hoebel, B. G.: Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. J. Neurosci. 15:6640–6650; 1995.
35. Purdy, M. B.; Lee, J. G.: The effect of restricted food intake, thiamin deficiency and riboflavin deficiency on the voluntary consumption of ethanol by the albino rat. Q. J. Stud. Alcohol 23:549–556; 1962.
36. Reicher, M. A.; Holman, O. E. W.: Location preference and flavor aversion reinforced by amphetamine in rats. Anim. Learn. Behav. 5:343–346; 1977.
37. Revusky, S.; Pohl, R. W.; Coombes, S.: Flavor aversions and deprivation state. Anim. Learn. Behav. 8:543–549; 1980.
38. Schafe, G. E.; Seeley, R. J.; Bernstein, I. L.: Forebrain contribution to the induction of a cellular correlate of conditioned taste aversion in the nucleus of the solitary tract. J. Neurosci. 15:6789–6796; 1995.
39. Stewart, R. B.; Grupp, L. A.: An investigation of the interaction between the reinforcing properties of food and ethanol using the place preference paradigm. Prog. Neuropsychopharmacol. 5:609–613; 1981.
40. Stewart, R. B.; Grupp, L. A.: Conditioned place aversion mediated by orally self-administered ethanol in the rat. Pharmacol. Biochem. Behav. 24:1369–1375; 1986.
41. Swank, M. W.; Schafe, G. E.; Bernstein, I. L.: c-*fos* induction in response to taste stimuli previously paired with amphetamine or LiCl during taste aversion learning. Brain Res. 673:251–261; 1995.
42. Takahashi, R. N.; Singer, G.: Effects of body weight levels on cannabis self-injection. Pharmacol. Biochem. Behav. 13:877–881; 1980.
43. Terroine, T.; Rochette, J.: Instinct, experience ou hasard dans le libre choix des rats entre une ration normale et une ration alcoolisee. Arch. Int. Pharmacodyn. Ther. 72:191–205; 1946.
44. Thiele, T. E.; Roitman, M. F.; Bernstein, I. L.: c-*fos* induction in rat brainstem in response to ethanol- and lithium chloride-induced conditioned taste aversions. Alcohol. Clin. Exp. Res. 20: 1023–1028; 1996.
45. Westerfield, W.; Lawrow, J.: The effects of caloric restriction and thiamin deficiency on the voluntary consumption of alcohol by rats. Q. J. Stud. Alcohol. 14:378–384; 1953.
46. White, N.; Sklar, L.; Amit, Z.: The reinforcing action of morphine and its paradoxical side effect. Psychopharmacology (Berlin) 52:63–66; 1977.
47. Winer, G. J.; Brown, D. R.; Michaels, K. M.: Statistical principles in experimental design, 3rd ed. New York: McGraw Hill.